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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
10/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,331	DEFREES ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-25* is/are pending in the application.

4a) Of the above claim(s) *14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 22, 2009 has been entered.

2. Claims 1 and 3-25 are pending.

3. Claims 14-25 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1 and 3-13, drawn to a compound having the formula: Ab-G-L-T, are being acted upon in this Office Action.

5. The disclosure is objected to under 37 CFR 1.71 for failing to provide antecedent basis for original claim. Specifically, the specification should provide clear support or antecedent basis for the term structures recited in original claim 11.

6. Rejections withdrawn.

7. The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Leung et al (of record, J Immunology 154: 5919-5926, 1995; PTO 1449) has been obviated by the applicant's argument that the reference does not teach intact glycosyl linking group, see page 12 of amendment. The reference glycosyl linking group has been oxidized (not degraded), see page 5920 col. 2, Carbohydrate modification.

8. The rejection of claims 1, 3-4, 7 and 9 under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,743,896 (of record, filed Sept 20, 2001 claimed earliest priority to June 23, 1997; PTO 892) has been obviated by the applicant's argument that the reference teaches an indirect method of attaching a toxin to an antibody (SCA) through a carrier polymer and a method of directly attaching a diagnostic or therapeutic agent to the glycosylated SCA. Both methods, however,

require oxidation, *i.e.* degradation, of an antibody carbohydrate component and would not yield an "intact glycosyl linking group" as recited in the present claims. *See* lines 20-31, Col. 29 of the '896 patent.

9. The rejection of claims 4-9 under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,635,603 (newly cited, issued June 3, 1997; PTO 892) been obviated by the applicant's argument at page 13 of the amendment. Specifically, Oxidation (or degradation) of the carbohydrate creates aldehyde carbonyl groups or ketone carbonyl groups that are free to react with the amine groups of, *e.g.* toxin carrier molecules, to form a conjugate. *See* lines 46-57, Col. 15 of the '603 patent. As such, the degraded carbohydrate does not form the intact glycosyl linking group of the present invention.

10. The rejection of claims 4 and 10-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been obviated by the applicants' argument that the specification at paragraphs [0087]-[0088].

11. Rejections maintain.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1 and 3-13 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of

representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, the claims encompass a genus of compound having the formula: Ab-G-L-T wherein Ab is any and all antibody, G is any intact glycosyl linking group covalently joining Ab to L, L is any bond or any spacer moiety such as any substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl and substituted or unsubstituted aryl moieties, such as any poly(ethylene glycol) moiety covalently joining G to T and T is any toxin.

Claims 4-6 encompass any compound having the structure as set forth in claim 4 wherein L1 is any bond or any linker moiety, A is any amplifier moiety, or any dendrimer, G is any antibody and T is any toxin.

At the time of filing, the specification discloses only the specific monoclonal antibodies that bind to RSV, IL-2 receptor, CEA, platelet IIb/IIIa receptor, EGF or HER-2 receptor covalently linked to toxin via O-glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM, sugar for targeting toxin to the specific tissue, see pages 19 and page 38.

The specification does not describe the *binding specificity* associated with the complete structure of any and all antibody for the claimed compound. The specification does not adequately describe the common structural attribute, i.e., antibody, intact glycosyl linking group other than the O-linked glycosylation site for an attachment of sugar selected from the group consisting of acetylgalactosamine, galactose, mannose, GlcNAc, glucose, fucose or xylose.

Witte et al (Cancer and Metastasis Reviews 17: 155-161, 1998; PTO 892) teach monoclonal antibody such as DC101 that binds to mouse VEGFR2 and blocks the binding of VEGF to its receptor; however, the same antibody does not even binds to human KDR (VEGFR2), much less VEGFR from other mammal, see abstract, in particular. Without guidance

as to the binding specificity of the antibody in the claimed compound, it is unpredictable which undisclosed antibody when linked to toxin via an intact glycosyl linking group is effective for treating cancer in humans by delivering the toxin to the right tissue or cell type.

Further, the state of the art at the time of filing is such that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (of record, Proc Natl Acad Sci USA 79: 1979-1983, 1982; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

Further, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody may adversely affect its activity. Likewise, fragments of the antibody may not retain the appropriate three-dimensional structures necessary to foster binding activity. There are also critical framework residues which are also important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and light chains. There is no guidance as to which residues in all antibodies and toxins the attachment site and whether the antibody retains antigen binding and the toxin activity remain uncompromised.

Further, there is no single species of antibody-toxin conjugate has been disclosed to have targeting toxin to the site of interest. There is insufficient description of a common core structure that would allow one of skill in the art to practice the invention as claimed. The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of antibody covalently linked to a genus of intact glycosyl linking group or to a genus of spacer moiety to a genus of toxin as claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1103, Friday April 11, 2004.

Applicants' arguments filed July 22, 2009 have been fully considered but are not found persuasive.

Applicants' position is that the intact glycosyl linking group is a separate moiety from the antibody portion of the claimed compound. Furthermore, the specification offers support for the inclusion of O-linked and/or N-linked glycosylation sites in the antibody amino acid sequence. *See* [0162] of the specification. As those of ordinary skill in the art will recognize and as exemplified in FIGs. 1-9, O- linked and N-linked glycosylation sites can be the points of attachment for either glycan chains *or* single sugar molecules. Armed with the present disclosure, those of ordinary skill in the art can readily appreciate what is encompassed by an "intact glycosyl linking group" and recognize what the applicant was in possession of. *See* [0051] of the specification. In view of the foregoing, Applicants respectfully submit that the written description requirement is satisfied for the pending claims.

In response, Claims 1 and 3 encompass a genus of compound having the formula: Ab-G-L-T wherein Ab is any and all antibody, G is any intact glycosyl linking group covalently joining

Ab to L, L is any bond or any spacer moiety such as any substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl and substituted or unsubstituted aryl moieties, such as any poly(ethylene glycol) moiety covalently joining G to T and T is any toxin.

Claims 4-6 encompass any compound having the structure as set forth in claim 4 wherein L1 is any bond or any linker moiety, A is any amplifier moiety, or any dendrimer, Ab is any and all antibody, G is any intact glycosyl linking group and T is any toxin.

At the time of filing, the specification discloses only antibody that binds to covalently linked to toxin via O-glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM, sugar for targeting toxin to the specific tissue, see pages 19 and 38.

The specification does not describe the *binding specificity* associated with a genus of antibody for the claimed compound other than the specific antibody that binds to CD20, CD3, TNF receptor, CD4, CEA, EGF or HER-2 receptor covalently linked to toxin via O-glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM.

Witte et al (Cancer and Metastasis Reviews 17: 155-161, 1998; PTO 892) teach monoclonal antibody such as DC101 that binds to mouse VEGFR2 and blocks the binding of VEGF to its receptor; however, the same antibody does not even binds to human KDR (VEGFR2), much less VEGFR from other mammal, see abstract, in particular. Without guidance as to the binding specificity of the antibody in the claimed compound, it is unpredictable which undisclosed antibody when linked to toxin via an intact glycosyl linking group is effective for treating cancer in humans by delivering the toxin to the right tissue or cell type.

Because the described antibody in the claimed compound is not representative of the entire claimed genus, one of skill in the art would conclude that applicant was not in procession of the claimed genus as a whole at the time of filing. Therefore, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 1 and 3-13.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. Further, possession may not be shown by merely described how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is

directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1 and 3-11 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 7,125,843 (of record, filed April 9, 2003 claimed earliest priority to Oct 10, 2001; PTO 892).

The applied reference has a common inventor Shawn DeFrees with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '843 patent teaches a compound such as an antibody conjugate comprising an antibody targeting moiety such as anti-CD20 antibody or HER2 (see col. 36, line 65, Figure 49A-51C col. 67, line 48-67, col. 143, line 34-41, col. 141, line 30-42, col. 339, line 1-13, in particular), an intact glycosyl linking group such as GlnNAc (see Fig 49A, in particular), joint to a spacer moiety such as sugar moiety GlcNAc-Man covalently joining to R such as toxin (See Fig 49A, 50A, 51A where the Y shape structure represents an antibody, intact glycosyl linking group such as sialyl group (Sia), glycosidic bond represent by the dash line, and toxin (R), claim 7 of the '843 patent, in particular). The reference glycosyl linking group is sialic acid residues such as (Sia)j (see FIG 49A, in particular) via a O-linked glycans originating from serine or threonine (see col. 12, line 33-35, col. 67, line 55-56, in particular) interposed between the antibody and the selected therapeutic moiety such as a toxin (R) or cytotoxic agents, e.g. adriamycin, doxorubicin

and taxol (see entire document col. 145, lines 66 through col. 146, line 5, col. 67, line 34-67, col. 67, line 18, col. 68, line 63, Table 2, col. 84, line 46-67, col. 166, line in particular).

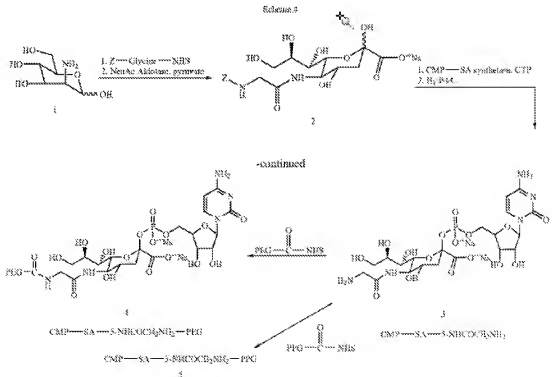
The term "or" in claim 1 does not require the spacer moiety such as substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl or substituted aryl moieties (See Fig 49A, 50A, 51A where the Y shape structure represents an antibody, intact glycosyl linking group is sialyl group (Sia), glycosidic bond represent by the dash line, and toxin (R), claim 7 of the '843 patent, in particular). The '843 patent further teaches various linker moiety such as intact glycosyl linking group such as cytidine monophosphoryl sialyl linked to toxin (see FIG 49B, CMP-SA-toxin, in particular) or UDP-Gal-toxin (see FIG 49C, in particular). The reference glycosyl linking group is intact because the use of galactosyltransferase for site specific enzymatic transfer of toxin to GAL, which does not require oxidation of carbohydrate portion of an antibody component.

The '843 patent further teaches the intact glycosyl linking group (see col. 45, lines 60 through col. 46, lines 1-21, in particular). The '843 patent further teaches the reference toxin include ricin or CC-105 (see col. 45, lines 59 through col. 47, lines 1-3, in particular). The reference amplifier moiety includes polyethylene glycol either linear or branched, alkyl, substituted and unsubstituted alkyl, substituted and unsubstituted aryl (see col. 75 line 8 through col. 78, lines 1-26, col. 68, line 13-15, in particular). The reference PEG spacer moiety can be linear or branched such as PEG comprises alkyl group (see col. 69, line 34-60, col. 75, line 66, col. 77, lines 7-8, in particular). The reference linker moiety can be alkyl, benzyl or aryl, substituted or unsubstituted thereof (see col. 77, line 23-32, in particular). The reference conjugate further comprises an amplifier moiety such as multiple PEG, polypropylene glycol (PPG) or alkylated amine (see col. 77, line 45-50, col. 147, line 46-52, in particular) or polyamine such as polylysine, polyaspartic acid, polyglutamate (see col. 75, line 20-21, col. 79, line 60-67, col. 166, lines 15-21, in particular) or dendrimer, poly(amino acid), polysaccharide or the like (see col. 69, paragraphs 457-459, in particular). The PEG linker that includes two glycosyl groups is for purposes of clarity and should not be interpreted as limiting the identity of linker arms of use in this embodiment of the invention. Thus, a PEG moiety is functionalized at a first terminus with a first glycosyl unit and at a second terminus with a second glycosyl unit. The first and second glycosyl units are preferably substrates for different transferases, allowing orthogonal attachment of the first and second peptides or antibodies to the first and second glycosyl units, respectively. In practice, the (glycosyl).sup.1-PEG-(glycosyl).sup.2 linker is contacted with the first peptide and a first transferase for which the first glycosyl unit is a substrate, thereby forming

(peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2. The first transferase and/or unreacted peptide or antibody is then optionally removed from the reaction mixture. The second peptide or antibody and a second transferase for which the second glycosyl unit is a substrate are added to the (peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2 conjugate, forming (peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2-(peptide).sup.2. Variety of linkers may be used in the bioconjugates such as homo and heterobifunctional crosslinkers, acid labile linker (cleavable bond) has the advantage where the conjugate is internalized in the endosomes or lysomes which have an acidic pH (see col. 143, lines 5-58, col. 173, lines 4-25, in particular).

Claim 10 is included in this rejection because the reference antibody is lined to a sugar via O-link to polymer such as polyethylene glycol that includes one or more (CH2)m from 0 to 20 and Z is a bond or OCH2CH2 (see col.75, lines 55 through col. 77, lines 61, col. 165, in particular) and a cleavable linker groups (see col. 173, lines 4-25, in particular).

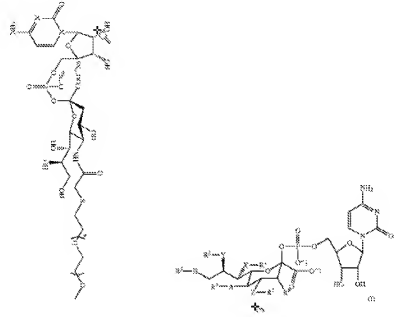
Claim 11 is included in this rejection because the reference formula 5 shows the claimed structure:



the mannosamine glycoside 1, is treated with the active ester of a protected amino acid (e.g., glycine) derivative, converting the sugar amine residue into the corresponding protected amino acid amide adduct. The adduct is treated with an aldolase to form the sialic acid 2. Compound 2 is converted to the corresponding CMP derivative by the action of CMP-SA synthetase, followed by

catalytic hydrogenation of the CMP derivative to produce compound 3. The amine introduced via formation of the glycine adduct is utilized as a locus of PEG or PPG attachment by reacting compound 3 with an activated PEG or PPG derivative (e.g., PEG-C(O)NHS, PPG-C(O)NHS), producing 4 or 5, respectively.

The modified sugar can also be



where X is a linking group, which is preferably selected from --O--, --N(H)--, --S, CH.sub.2--, and N(R).sub.2, in which each R is a member independently selected from R.sup.1 R.sup.5. "i" may be Na or another salt, and Na may be interchangeable with "i:The symbols Y, Z, A and B each represent a group that is selected from the group set forth above for the identity of X. X, Y, Z, A and B are each independently selected and, therefore, they can be the same or different. The symbols R.sup.1, R.sup.2, R.sup.3, R.sup.4 and R.sup.5 represent H, polymers, a water-soluble polymer, therapeutic moiety, biomolecule or other moiety. The symbol R6 represents H, OH, or a polymer. Alternatively, these symbols represent a linker that is linked to a polymer, water-soluble polymer, therapeutic moiety, biomolecule or other moiety.

It is clear to one of skill in the art knows how to design other useful glycans and pegylated antibody toxin using site-specific glycoconjugation enzyme such as glycotransferase that will target toxin or therapeutic to a specific tissue or cell for therapeutic use (see col. 64, lines 43-55, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed July 22, 2009 have been fully considered but are not found persuasive.

Applicants' position is the Office Action has not pointed to any portion of DeFrees *et al.* disclosing the formula Ab-G-L-T nor has the Examiner shown how one of ordinary skill in the art

could immediately envisage an [antibody]-[intact glycosyl linking group]-[bond/spacer]-[toxin] compound in U.S. 7,125,843.

Contrary to applicants' assertion that the claims are not properly rejected, in addition to the generic formula, applicants' attention is directed to various Figures in the patent such as Figure 49A, 50A, and 51A where the Y shape structure represents an antibody, sialyl group (Sia) on the sugar Gal represents intact glycosyl group, the dash represent glycosidic bond or spacer, and R represents the toxin, claim 7 of the '843 patent, in particular). The '843 patent further teaches various linker moiety such as intact glycosyl linking group such as cytidine monophosphoryl sialyl linked to toxin (see FIG 49B, CMP-SA-toxin, in particular), UDP-Gal linked to Toxin (see Figure 49C, UDP-Gal-Toxin, in particular). The term "or" in claim 1 does not require the spacer moiety such as substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl or substituted aryl moieties (See Fig 49A, 50A, 51A, in particular). The reference antibody such as Herceptin.TM. is expressed in a mammalian system and is first galactosylated using a galactose donor and a galactosyltransferase. Herceptin.TM. is then conjugated with a toxin via a sialic acid through the action of ST3Gal3 using a reactive sialic acid-toxin complex. In FIG. 49C, Herceptin™ produced in either mammalian cells or fungi and is conjugated to a toxin through the process of galactosylation, using a galactosyltransferase and a reactive galactose-toxin complex. FIG. 49D contains another scheme of making Herceptin.TM. conjugates: Herceptin.TM. produced in fungi is first treated with Endo-H to trim back glycosyl groups, then galactosylated using a galactose donor and a galactosyltransferase, and then conjugated with a radioisotope by way of sialylation, by using ST3Gal3 and a reactive sialic acid-radioisotope complex. By using various enzymes converting the precursor to said glycosyl linking group, thereby forming said covalent conjugate. As such, the reference glycosyl linking group is not oxidized and therefore "intact".

Further, the generic formula also applies to the claimed invention because the peptide could be an antibody, the sugar on the antibody such as galactose, mannose, GlcNAc, Glucose, Fucose, the linker represents by sialyl group (Sia), amplifier moiety is the polysaccharide such as mannose (see Figure 49A, Man), a polymer such as polyethylene glycol moiety (see col. 68, line 13-15, in particular). The reference PEG spacer moiety can be linear or branched such as PEG comprises alkyl group (see col. 69, line 34-60, col. 75, line 66, col. 77, lines 7-8, in particular). The reference linker moiety can be alkyl, benzyl or aryl (see col. 77, line 23-32, in particular). The reference conjugate further comprises an amplifier moiety such as multiple PEG,

polypropylene glycol (PPG) or alkylated amine (see col. 77, line 45-50, col. 147, line 46-52, in particular) or polyamine such as polylysine, polyaspartic acid, polyglutamate (see col. 75, line 20-21, col. 79, line 60-67, col. 166, lines 15-21, in particular). Those of skill in the art will appreciate that the conjugates between more than two peptides by, for example, by the use of a branched PEG, dendrimer, poly(amino acid), polysaccharide or the like (see col. 69, paragraphs 457-459, in particular), follows by the agent such as toxin, drug, radioisotope complex.

16. New ground of rejection.

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1 and 3-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a compound having the formula: Ab--G--L--T wherein Ab is an antibody that binds to RSV, IL-2 receptor, CEA, platelet IIb/IIIa receptor, EGF or HER-2 receptor, G is an intact glycosyl linking group covalently joining Ab to L; L is a bond or a spacer moiety covalently joining G to T; and T is a toxin, wherein said spacer moiety is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl and substituted or unsubstituted aryl moieties, **does not** reasonably provide enablement for how to use such compound as set forth in claims 1 and 3-13 without guidance as to the binding specificity of such antibody in the claimed compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompassed innumerous antibody covalently linked to any and all toxin via any intact glycosyl linking group and bond or spacer moiety or amplifier moiety for the claimed compound.

Enablement is not commensurate in scope with how to use any compound as set forth in claims 1 and 3-13 without guidance as to the binding specificity of such antibody in the claimed compound for targeting toxin.

At the time of filing, the specification discloses only the specific monoclonal antibodies that bind to RSV, IL-2 receptor, CEA, platelet IIb/IIIa receptor, EGF or HER-2 receptor covalently linked to toxin via O-glycosylation through an intact glycosyl linking group and a spacer such as polyethylene glycol, polylysine, or dendrimer PAMAM, for targeting toxin to the specific cell or tissue, see pages 19 and 38.

The specification does not teach how to use any and all compound comprising any antibody other than the specific antibody mentioned above covalently linked to toxin via O-glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM for targeting toxin to the tumor or tumor surrounding tissue.

The specification does not teach the *binding specificity* associated with the structure of any and all antibody for the claimed compound.

Witte et al (Cancer and Metastasis Reviews 17: 155-161, 1998; PTO 892) teach monoclonal antibody such as DC101 that binds to mouse VEGFR2 and blocks the binding of VEGF to its receptor; however, the same antibody does not even binds to human KDR (VEGFR2), much less VEGFR from other mammal, see abstract, in particular. Without guidance as to the binding specificity of the antibody in the claimed compound, it is unpredictable which undisclosed antibody when linked to toxin via an intact glycosyl linking group is effective for treating cancer in humans by delivering the toxin to the right tissue or cell type.

Methods for antibody and binding fragment were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for using any and all antibody with an expectation that any antibody is useful for treating any disease such as cancer when linked to toxin.

Vitetta et al (Science 313: 308-309, 2006; PTO 892) teach given the complex structure of antibodies, designing therapeutic antibodies can be unpredictable; in the case of anti-CD28 antibody, although preclinical data show that the antibody was safe when administered to two species of monkeys, healthy human injected with the anti-CD28 antibody suffered immediate and profound side effects (see pages 308-309, in particular).

Therefore, it is unpredictable whether any and all compound comprising any antibody linked to any toxin via an intact glycosyl linking group and spacer moiety or amplifier moiety can be used as a pharmaceutical composition for treating any diseases *in vivo*.

Given the genus of antibody in the claimed compound, the lack of *in vivo* working example, it is unpredictable which undisclosed antibody when linked to any and all toxin is useful for treating any and all diseases. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
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